

AMENDMENTS TO THE SPECIFICATION

Please make the following amendments to the specification

On Page 3, lines 17-18, please insert "In accordance with the invention, an injection molded capsule shell, and/or linker is provided for with a composition including Eudragit ® 4135F."

On Page 3, the paragraph starting on lines 19-26 please insert

The capsule shell or linker comprises a solid matrix, and composed of Eudragit ® 4135F present in an amount of about 20 to 70% w/w, and a hydroxypropyl cellulose derivative, or blend of hydroxypropylcellulose derivatives, present from about 20 to about 70% w/w. The composition may optionally further comprises dissolution-modifying excipients present in an amount of about 0% w/w to about 30% w/w; a lubricant present in an amount up to about 30% w/w; a plasticizer present in an amount up to about 10% w/w, and a processing agent present in an amount up to about 10% w/w.

On Page 4, the paragraph starting on lines 13-19 please insert

The present invention also relates to the application of a pharmaceutically acceptable film coating over a component comprising the novel pharmaceutically acceptable polymeric blends as described herein. The film coating may be a delayed release formulation, or a pH control formulation as are well known in the art. One suitable coating is Eudragit® L30D-55. The enteric coatings may be applied using standard equipment such as a GMP Aerocoater column coater. The component weight gain is nominally from about 3% to about 5% w/w.

On Page 6, the paragraph starting on lines 1-15 please insert

line 10) being a copolymer of methacrylic acid, methyl methacrylate and methyl acrylate (suitably in a ratio of 10:25:65) has been found to be a preferred polymer for use in the present invention. This ratio of components is also known as Eudragit® 4135F, and is a solid product obtained from Eudragit® FS 30D, and as noted above is available from Rohm Pharma/ Degussa, Darmstadt, Germany. However, it has been found that the unblended polymer alone is not suitable for injection molding, but must be blended in accordance with the teachings herein to produce suitable injection molded, non-distorted, unwarped capsule/sub-unit components for assembly into either single capsule or multicompartment dosage forms. For purposes herein, Eudragit® 4135F and various derivatives blends of similar ratios of components, i.e., copolymer blends of methacrylic acid, methyl methacrylate and methyl acrylate, such as 10 to 40% w/w methacrylic acid; 30-80% methyl acrylate; and

0 to 40% methyl methacrylate, including but not limited to those described in US 5,705,189 as E1 and E3 emulsion polymers. Eudragit® 4135F has an average molecular weight of about 220,000.

On Page 6, the paragraph starting on lines 29-37 please insert

As noted, Eudragit® 4135F hydrates and begins to erode above a pH of 7.2. It has been found that there is a large intersubject variation of the intestinal luminal pH, and that it is difficult to achieve significant exposure to the capsule walls for the required pH in a large number of patients. Further, a shell wall thickness of 0.5mm produces results which have a prolonged dissolution time for the unmodified polymer (>30hrs). Consequently, to achieve a pulsatile release with this polymer in an injection molded shell, various excipients are needed in the formulation. Such agents include, but are not limited to, swelling agents, such as HPMC and super disintegrants; surfactants, such as SDS or the Pluronic groups; pore-

On Page 7, the paragraph starting on lines 5-22 please make the following changes:

A preferred co-blend with Eudragit® 4135F is the polymer HPC. One suitable brand is that marketed by Aqualon, a division of Hercules Incorporated, as Klucel®. Klucel® HPC is produced in various grades, as determined by their intended use. The Klucel® polymers of choice are Klucel® EF, Klucel® JH, Klucel® LF, and Klucel® GF, or combinations thereof. It is recognized that other Klucel polymers may be used in combination with a lower molecular weight polymer to produce a blended ingredient for use herein. Klucel® E has a viscosity in the range of 150-700 (a 200-600 mPas at a 10% concentration in aqueous solution at 25 °C for EF pharm; 300-600 mPas for EXF Pharm), and a molecular weight of about 80,000; JF has a viscosity of 150-400 mPas at 5% concentration in aqueous solution at 25 °C, and a molecular weight of about 140,000, LF has a viscosity in the range of 75 –150 mPas at a 5% concentration in aqueous solution at 25 °C, and a molecular weight of about 95,000; GF has a viscosity in the range of 150–400 mPas at a 2% concentration in aqueous solution at 25 °C, and a molecular weight of about 370,000; Klucel® M has a molecular weight of about 850,000 and a viscosity in the range of 4000-6500 mPas at a 2% concentration in aqueous solution at 25 °C; and Klucel® H as a molecular weight of about 1,150,00 and a viscosity in the range of 1500-3000 mPas at a 1% concentration in aqueous solution at 25 °C.

On Page 8, the paragraph starting on lines 32-34 please make the following changes:

The polymer polymethacrylate, Eudragit® 4135F is present in the formulation in an amount of about 20 to about 90% w/w, preferably from about 20 to about 40% w/w.

On Page 9, the paragraph starting on lines 1-3 please make the following changes:

to 70% overall w/w amount. In one embodiment of the present invention the compositions of Eudragit® 4135F comprise a blend of at least two hydroxypropylcellulose polymers of differing molecular weights.

On Page 11, the paragraph starting on lines 1-4, please make the following changes:

w/w. Preferably, the plasticizer may be present from about 0 about 5% w/w. In one embodiment of the present invention, the ability to form an injection molded shell of a Eudragit® 4135F formulation without the addition of a plasticizer such as those noted above may be achieved.

On Page 12, the paragraph starting on lines 32-36, please make the following changes:

One embodiment of the present invention is the combination of a stearyl alcohol, a swellable solid, sodium starch glycolate and/or croscarmellose sodium; the polymer hydroxypropylcellulose or blends of HPC, a surfactant, and the polymer Eudragit® 4135F or a similar co-polymer blend. Suitably, if the surfactant is SDS it is present at 2% w/w or less, more preferably 1% or less, and less than <20% w/w

On Page 17, the paragraph starting on lines 5-12, please make the following changes:

For production of an early release capsule or component in a multidosage capsule, (such as in a 2 hour window), the polymer Eudragit® 4135F (Röhm), may be extruded into a thin walled component shell (such as those indicated herein), by blending with several excipients as noted herein. As will be seen by the experimental section, formulation with a lubricant, and a co-blend of hydroxypropyl cellulose has now been shown to produce a stable, injection molded component which can be reliably reproduced and injected from the mold with reduced, or no warpage of the shell.

On Page 17, the paragraph starting on lines 16-22, please make the following changes:

Experiments with Klucel® HPC at various percentages, ranging from 30 to 70% have been formulated and tested for the variance in dissolution times. Formulations containing 30 to 60 % Klucel® have been found to have similar dissolutions times (<2hours) in both simulated gastric fluid and simulated intestinal fluids. Dissolutions times for formulations containing less than 30% Klucel® are longer and more variable indicating that an increased level of greater than 40% of Klucel® is necessary to provide reproducible release profiles.

On Page 17, the paragraph starting on lines 23-36, please make the following changes:

To ensure a slower release, the pharmaceutical formulations include various hydrophilic excipients. Preferably, the hydrophilic excipient is one which does not melt at the extrusion temperature, e.g. the lactose, inorganic salts, HPC, HPMC, such as Pharmacoat 603 (an HPMC with a glass transition temperature of about 175°C). In another embodiment copovidone has also been found to be a useful ingredient with Eudragit® F4135, along with HPMC, as well as other cellulose or swellable agents. As noted, these swellable solids are available commercially in a number of grades by molecular weight, for examples 95K, or 80K grades of HPC. A change in the molecular weight of HPC, for instance, should retain the ability to hydrate the shell, but the hydration rate may be slower, i.e. the rate of expansion will be reduced. Hence, a longer dissolution time of the shell and release of the components therein may result. Experiments with Klucel® HPC at various percentages, and with differing molecular weights have been formulated and tested for the variance in dissolution times. Formulations containing 40 to 70 % Klucel®

On Page 18, the paragraph starting on lines 21-35, please make the following changes:

Formulations containing Eudragit® 4135F and hydroxypropylcellulose (various molecular weight combinations of Klucel®) were extruded, pelletised and then injection moulded.

	Ex. 1	Ex. 2	Ex. 3
Component	-----%w/w-----		
Eudragit®4135F	24.0	24.0	24.0
Stearyl alcohol	12.0	12.0	12.0
Klucel ®EF	30.0	30.0	0.0
<i>Klucel® JF</i>	<i>30.0</i>	<i>0.0</i>	<i>30.0</i>
<i>Klucel® GF</i>	<i>0.0</i>	<i>30.0</i>	<i>30.0</i>
Explotab	2.0	2.0	2.0
SDS	1.0	1.0	1.0
Pluronic F68	<u>1.0</u>	<u>1.0</u>	<u>1.0</u>
	100	100	100

On Page 19, the paragraph starting on lines 10-12, please make the following changes:

Example 4

Formulation	
	%w/w
Eudragit® 4135F	24.00
Klucel ®LF	30.00
Klucel ®JF	30.00
Stearyl alcohol	12.00
Explotab	2.00
Texapon K-12	1.00
Pluronic F68	1.00

On Page 19, the paragraph starting on lines 15-17, please make the following changes:

Example 5

Formulation	
	%w/v
Eudragit <u>®</u> 4135F	24.00
Klucel <u>®</u> LF	30.00
Klucel <u>®</u> GF	30.00
Stearyl alcohol	12.00
Explotab	2.00
Texapon K-12	1.00
Pluronic F68	1.00

On Page 20, the paragraphs starting on lines 2-5, please make the following changes:

Example 6

Formulation	
	%w/v
Eudragit <u>®</u> 4135F	24.00
Klucel <u>®</u> JF	30.00
Klucel <u>®</u> GF	30.00
Stearyl alcohol	12.00
Explotab	2.00
Texapon K-12	1.00
Pluronic F68	1.00

On Page 20, the paragraphs starting on lines 9-11, please make the following changes:

Example 7

Formulation	
	%w/w
Eudragit <u>®</u> 4135F	24.00
Klucel <u>®</u> EF	32.00
Klucel <u>®</u> JF	32.00
Stearyl alcohol	12.00

On Page 20, the paragraphs starting on lines 14-20, please make the following changes:

The 0.5mm shells produced under this Example were tested using USP3 dissolution ~~apparatus~~ apparatus at a dip speed of 5 dips per minute (dpm). The samples all release between 45 –60 minutes in a USP3, and after 2 hours all the shells have become completely detached from the linker (Eudragit® 4135F/10% pharmacoat/12% stearyl alcohol). The release mechanism appears to be swelling of the matrix over a period of time, detachment appears to be largely independent of the weld conditions used to seal the units.

On Page 20, the paragraphs starting on lines 1-3, please make the following changes:

Example 8

Formulation	
	%w/v
Eudragit® 4135F	29.00
Klucel ®EF	25.00
Klucel ®JF	30.00
Stearyl alcohol	12.00
Explotab	2.00
Texapon K-12	1.00
Pluronic F68	1.00

On Page 20, the paragraphs starting on lines 8-10, please make the following changes:

Example 9

Formulation	
	%w/v
Eudragit ®4135F	10.00
Klucel ®EF	70.00
Stearyl alcohol	12.00
Explotab	5.00
Texapon K-12	1.00
Pluronic F68	2.00

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On Page 22, the paragraphs starting on lines 1-3, please make the following changes:

Example 10

Formulation	
	%w/v
Eudragit® 4135F	10.00
Klucel ®LF	70.00
Stearyl alcohol	12.00
Explotab	5.00
Texapon K-12	1.00
Pluronic F68	2.00

On Page 22, the paragraphs starting on lines 7-10, please make the following changes:

Example 11

Formulation	
	%w/w
Eudragit ®4135F	15.00
Klucel ®EF	55.00
Stearyl alcohol	12.00
Explotab	2.00
Texapon K-12	1.00
Lactose	15.00

On Page 23, the paragraphs starting on lines 1-4, please make the following changes:

Example 12

Formulation	
	%w/w
Eudragit <u>®</u> 4135F	15.0
Klucel <u>®</u> EF	55.0
Stearyl alcohol	12.0
Explotab	2.0
Texapon K-12	1.0
Mannitol	15.0

On Page 22, the paragraphs starting on lines 11-13, please make the following changes:

Example 13

Formulation	
	%w/w
Eudragit <u>®</u> 4135F	15.0
Klucel <u>®</u> EF	55.0
Stearyl alcohol	12.0
Explotab	2.0
Texapon K-12	1.0
Mannitol	15.0

On Page 24, the paragraphs starting on lines 1-7, please make the following changes:

“found to be extremely flexible, a quality attributed to the presence of Klucel® in the blend.

Formulations of Example 1 and Example 2 were tested using the USP3 dissolution apparatus. The shells were ultrasonically welded to a Eudragit® 4135F / 10% Pharmacoat / 12% Stearyl alcohol linker using a maximum weld strength. All but one sample released at approximately 1.5hrs. There did not appear to be a significant difference in release time between the two formulations.”

On Page 19, the paragraphs starting on lines 1-8, please make the following changes:

Example 14

Using shells produced in accordance with Example 7, the 0.3 mm shells were film coated with 5%, 10%, and 15% Eudragit® L30D-55 as an enteric coat in an Aeromatic Aerocoater. The dissolution results indicate that the 15% enteric coat provides the necessary delay in release along with the most reproducible release times. The release was determined to be about 2 hours +/- 20 min for 11 of the 12 samples tested.